C7 ESTER SUBSTITUTED TAXANES

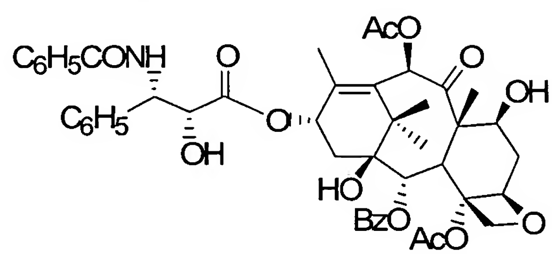
REFERENCE TO RELATED APPLICATION

This application claims priority from U.S. provisional application Serial No. 60/179,794, filed on February 2, 2000.

BACKGROUND OF THE INVENTION

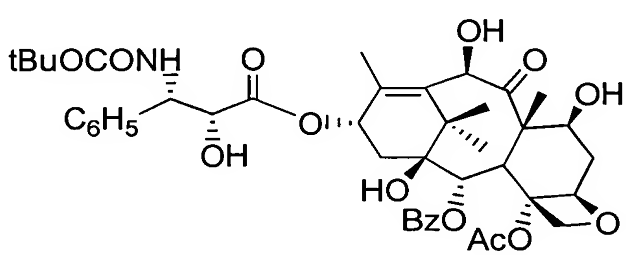
The present invention is directed to novel taxanes which have exceptional utility as antitumor agents.

The taxane family of terpenes, of which baccatin III and taxol are members, has been the subject of considerable interest in both the biological and chemical arts. Taxol itself is employed as a cancer chemotherapeutic agent and possesses a broad range of tumor-inhibiting activity. Taxol has a 2′R, 3′S configuration and the following structural formula:



wherein Ac is acetyl.

Colin et al. reported in U.S. Patent 4,814,470 that certain taxol analogs have an activity significantly greater than that of taxol. One of these analogs, commonly referred to as docetaxel, has the following structural formula:



Although taxol and docetaxel are useful chemotherapeutic agents, there are limitations on their effectiveness, including limited efficacy against certain types of cancers and toxicity to subjects when administered at various doses.

Accordingly, a need remains for additional chemotherapeutic agents with improved efficacy and less toxicity.

SUMMARY OF THE INVENTION

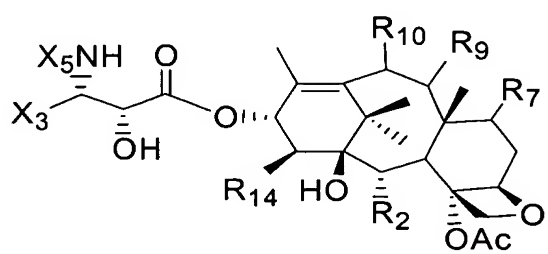
Among the objects of the present invention, therefore, is the provision of taxanes which compare favorably to taxol and docetaxel with respect to efficacy as anti-tumor agents and with respect to toxicity. In general, these taxanes possess an ester substituent other than formate, acetate and heterosubstituted acetate at C-7, a hydroxy substituent at C-10 and a range of C-3' substituents.

Briefly, therefore, the present invention is directed to the taxane composition, per se, to pharmaceutical compositions comprising the taxane and a pharmaceutically acceptable carrier, and to methods of administration.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one embodiment of the present invention, the taxanes of the present invention correspond to structure (1):



(1)

wherein

R_2 is acyloxy;

R_7 is R_{7a}COO-;

R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon of which R_{7a} is a substituent;

R_9 is keto, hydroxy, or acyloxy;

R_{10} is hydroxy;

R_{14} is hydrido or hydroxy;

X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, phenyl or heterocyclo;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo;

Ac is acetyl; and

R_7, R_9, and R_{10} independently have the alpha or beta stereochemical configuration.

In one embodiment, R_2 is an ester ($R_{2a}C(O)O$-), a carbamate ($R_{2a}R_{2b}NC(O)O$-), a carbonate ($R_{2a}OC(O)O$-), or a thiocarbamate ($R_{2a}SC(O)O$-) wherein R_{2a} and R_{2b} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocyclo. In a preferred embodiment, R_2 is an ester ($R_{2a}C(O)O$-), wherein R_{2a} is aryl or heteroaromatic. In another preferred embodiment, R_2 is an ester ($R_{2a}C(O)O$-), wherein R_{2a} is substituted or unsubstituted phenyl, furyl, thienyl, or pyridyl. In one particularly preferred embodiment, R_2 is benzoyloxy.

In one embodiment, R_7 is $R_{7a}COO$- wherein R_{7a} is (i) substituted or unsubstituted C_2 to C_8 alkyl (straight, branched or cyclic), such as ethyl, propyl, butyl, pentyl, or hexyl; (ii) substituted or unsubstituted C_2 to C_8 alkenyl (straight, branched or cyclic), such as ethenyl, propenyl, butenyl, pentenyl or hexenyl; (iii) substituted or unsubstituted C_2 to C_8 alkynyl (straight or branched) such as ethynyl, propynyl, butynyl, pentynyl, or hexynyl; (iv) substituted or unsubstituted phenyl; or (v) substituted or unsubstituted heteroaromatic such as furyl, thienyl, or pyridyl. The substituents may be hydrocarbyl or any of the heteroatom containing substituents identified elsewhere herein for substituted hydrocarbyl. In a preferred embodiment, R_{7a} is ethyl, straight, branched or cyclic propyl, straight, branched or cyclic butyl, straight, branched or cyclic pentyl, straight, branched or cyclic hexyl, straight or branched propenyl, isobutenyl, furyl or thienyl. In another embodiment, R_{7a} is substituted ethyl, substituted propyl (straight, branched or cyclic), substituted propenyl (straight or branched), substituted isobutenyl, substituted furyl or substituted thienyl wherein the substituent(s) is/are selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

While R_9 is keto in one embodiment of the present invention, in other embodiments R_9 may have the alpha or beta stereochemical configuration, preferably the beta stereochemical configuration, and may be, for example, α- or

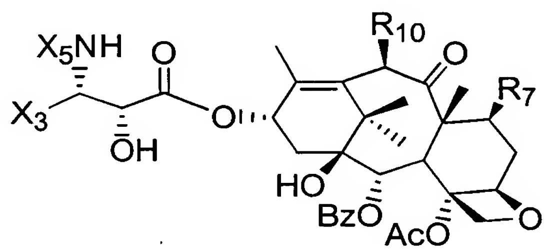
β-hydroxy or α- or β-acyloxy. For example, when R_9 is acyloxy, it may be an ester ($R_{9a}C(O)O$-), a carbamate ($R_{9a}R_{9b}NC(O)O$-), a carbonate ($R_{9a}OC(O)O$-), or a thiocarbamate ($R_{9a}SC(O)O$-) wherein R_{9a} and R_{9b} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocyclo. If R_9 is an ester ($R_{9a}C(O)O$-), R_{9a} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaromatic. Still more preferably, R_9 is an ester ($R_{9a}C(O)O$-), wherein R_{9a} is substituted or unsubstituted phenyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, or substituted or unsubstituted pyridyl. In one embodiment R_9 is ($R_{9a}C(O)O$-) wherein R_{9a} is methyl, ethyl, propyl (straight, branched or cyclic), butyl (straight, branched or cyclic), pentyl, (straight, branched or cyclic), or hexyl (straight, branched or cyclic). In another embodiment R_9 is ($R_{9a}C(O)O$-) wherein R_{9a} is substituted methyl, substituted ethyl, substituted propyl (straight, branched or cyclic), substituted butyl (straight, branched or cyclic), substituted pentyl, (straight, branched or cyclic), or substituted hexyl (straight, branched or cyclic) wherein the substituent(s) is/are selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

Exemplary X_3 substituents include substituted or unsubstituted C_2 to C_8 alkyl, substituted or unsubstituted C_2 to C_8 alkenyl, substituted or unsubstituted C_2 to C_8 alkynyl, substituted or unsubstituted heteroaromatics containing 5 or 6 ring atoms, and substituted or unsubstituted phenyl. Exemplary preferred X_3 substituents include substituted or unsubstituted ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclohexyl, isobutenyl, furyl, thienyl, and pyridyl.

Exemplary X_5 substituents include $-COX_{10}$, $-COOX_{10}$ or $-CONHX_{10}$ wherein X_{10} is substituted or unsubstituted alkyl, alkenyl, phenyl or heteroaromatic. Exemplary preferred X_5 substituents include $-COX_{10}$, $-COOX_{10}$ or $-CONHX_{10}$ wherein X_{10} is (i) substituted or unsubstituted C_1 to C_8 alkyl such as substituted or unsubstituted methyl, ethyl, propyl (straight, branched or cyclic), butyl (straight, branched or cyclic), pentyl (straight, branched or cyclic), or hexyl (straight, branched or cyclic); (ii) substituted or unsubstituted C_2 to C_8 alkenyl such as substituted or unsubstituted ethenyl, propenyl (straight, branched or cyclic), butenyl (straight, branched or cyclic), pentenyl (straight, branched or cyclic) or hexenyl (straight, branched or cyclic); (iii) substituted or unsubstituted C_2 to C_8 alkynyl such as substituted or unsubstituted ethynyl, propynyl (straight or

branched), butynyl (straight or branched), pentynyl (straight or branched), or hexynyl (straight or branched); (iv) substituted or unsubstituted phenyl, or (v) substituted or unsubstituted heteroaromatic such as furyl, thienyl, or pyridyl, wherein the substituent(s) is/are selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

In one preferred embodiment, the taxanes of the present invention correspond to the following structural formula (2):



(2)

wherein

R_7 is $R_{7a}COO$-;

R_{10} is hydroxy;

X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, or heterocyclo;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo;

R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon of which R_a is a substituent;

Bz is benzoyl; and

Ac is acetyl.

For example, in this preferred embodiment in which the taxane corresponds to structure (2), R_{7a} may be substituted or unsubstituted ethyl, propyl or butyl, more preferably substituted or unsubstituted ethyl or propyl, still more preferably substituted or unsubstituted ethyl, and still more preferably unsubstituted ethyl. While R_{7a} is selected from among these, in one embodiment X_3 is selected from substituted or unsubstituted alkyl, alkenyl, phenyl or heterocyclo, more preferably substituted or unsubstituted alkenyl, phenyl or heterocyclo, still more preferably substituted or unsubstituted phenyl or heterocyclo, and still more preferably

heterocyclo such as furyl, thienyl or pyridyl. While R_{7a} and X_3 are selected from among these, in one embodiment X_5 is selected from -COX_{10} wherein X_{10} is phenyl, alkyl or heterocyclo, more preferably phenyl. Alternatively, while R_{7a} and X_3 are selected from among these, in one embodiment X_5 is selected from -COX_{10} wherein X_{10} is phenyl, alkyl or heterocyclo, more preferably phenyl, or X_5 is -$COOX_{10}$ wherein X_{10} is alkyl, preferably t-butyl. Among the more preferred embodiments, therefore, are taxanes corresponding to structure 2 in which (i) X_5 is -$COOX_{10}$ wherein X_{10} is tert-butyl or X_5 is -COX_{10} wherein X_{10} is phenyl, (ii) X_3 is substituted or unsubstituted cycloalkyl, alkenyl, phenyl or heterocyclo, more preferably substituted or unsubstituted isobutenyl, phenyl, furyl, thienyl, or pyridyl, still more preferably unsubstituted isobutenyl, furyl, thienyl or pyridyl, and (iii) R_{7a} is unsubstituted ethyl or propyl, more preferably ethyl.

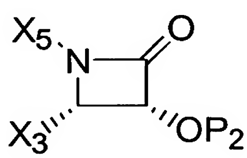
Among the preferred embodiments, therefore, are taxanes corresponding to structure 1 or 2 wherein R_7 is $R_{7a}COO$- wherein R_{7a} is ethyl. In this embodiment, X_3 is preferably cycloalkyl, isobutenyl, phenyl, substituted phenyl such as p-nitrophenyl, or heterocyclo, more preferably heterocyclo, still more preferably furyl, thienyl or pyridyl; and X_5 is preferably benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl. In one alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydrido. In another alternative of this embodiment, X_3 is

heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydrido. In each of the alternatives of this embodiment when the taxane has structure 1, R_7 and R_{10} may each have the beta stereochemical configuration, R_7 and R_{10} may each have the alpha stereochemical configuration, R_7 may have the alpha stereochemical configuration while R_{10} has the beta stereochemical configuration or R_7 may have the beta stereochemical configuration while R_{10} has the alpha stereochemical configuration.

Also among the preferred embodiments are taxanes corresponding to structure 1 or 2 wherein R_7 is R_{7a}COO- wherein R_{7a} is propyl. In this embodiment, X_3 is preferably cycloalkyl, isobutenyl, phenyl, substituted phenyl such as p-nitrophenyl, or heterocyclo, more preferably heterocyclo, still more preferably furyl, thienyl or pyridyl; and X_5 is preferably benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl. In one alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydrido. In another alternative of this embodiment, X_3 is

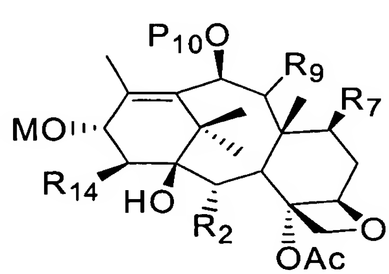
heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydrido. In each of the alternatives of this embodiment when the taxane has structure 1, R_7 and R_{10} may each have the beta stereochemical configuration, R_7 and R_{10} may each have the alpha stereochemical configuration, R_7 may have the alpha stereochemical configuration while R_{10} has the beta stereochemical configuration or R_7 may have the beta stereochemical configuration while R_{10} has the alpha stereochemical configuration.

Taxanes having the general formula 1 may be obtained by treatment of a β-lactam with an alkoxide having the taxane tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a β-amido ester substituent at C-13 (as described more fully in Holton U.S. Patent 5,466,834), followed by removal of the hydroxy protecting groups. The β-lactam has the following structural formula (3):



(3)

wherein P_2 is a hydroxy protecting group and X_3 and X_5 are as previously defined and the alkoxide has the structural formula (4):



(4)

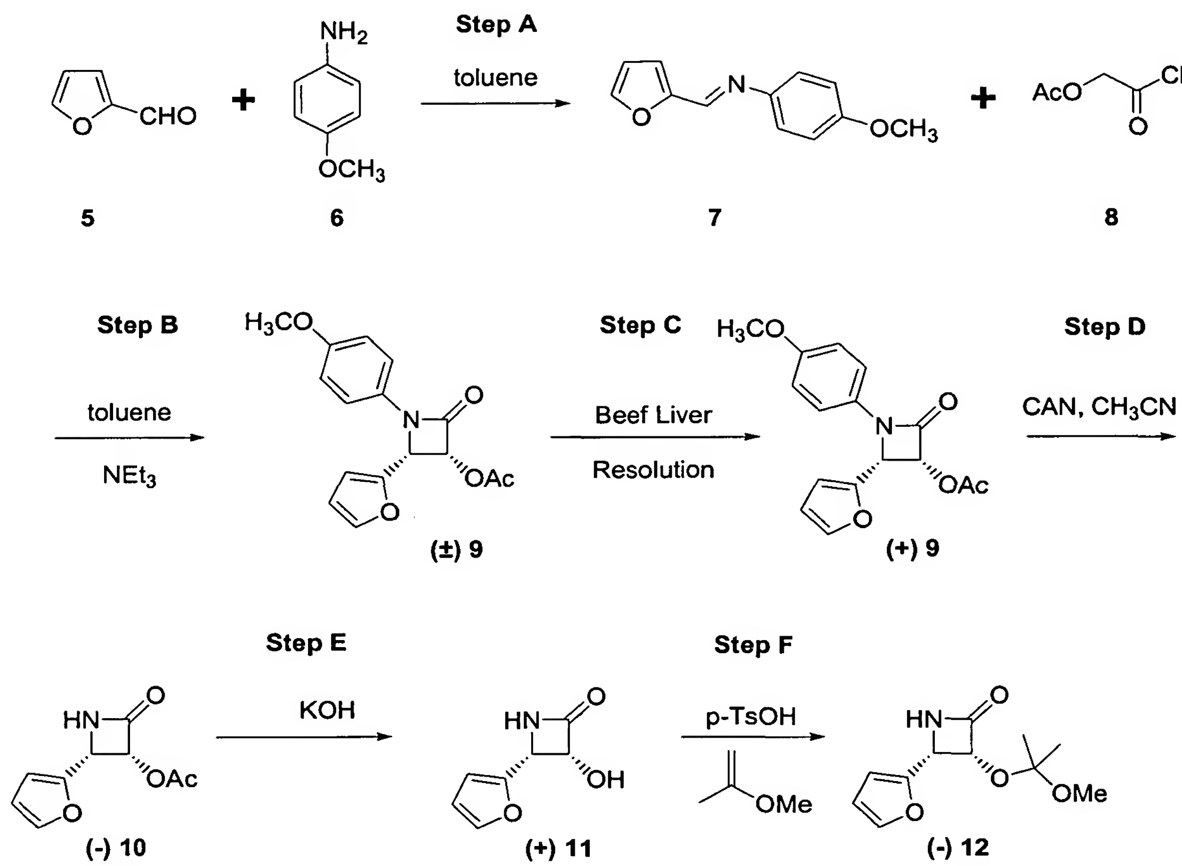
wherein M is a metal or ammonium, P_{10} is a hydroxy protecting group and R_2, R_9, R_7 and R_{14} are as previously defined.

Alkoxide 4 may be prepared from 10-deacetylbaccatin III (or a derivative thereof) by selective protection of the C-10 hydroxyl group and then esterification of the C-7 hydroxyl group followed by treatment with a metallic amide. In one embodiment of the present invention, the C(10) hydroxyl group of 10-deacetylbaccatin III is selectively protected with a silyl group using, for example, a silylamide or bissilyamide as a silylating agent. Preferred silylating agents include tri(hydrocarbyl)silyl-trifluoromethylacetamides and bis tri(hydrocarbyl)-silyltrifluoromethylacetamides (with the hydrocarbyl moiety being substituted or unsubstituted alkyl or aryl) such as N,O-bis-(trimethylsilyl) trifluoroacetamide, N,O-bis-(triethylsilyl)trifluoroacetamide, N-methyl-N-triethylsilyltrifluoroacetamide, and N,O-bis(t-butyldimethylsilyl)trifluoroacetamide. The silylating agents may be used either alone or in combination with a catalytic amount of a base such as an alkali metal base. Alkali metal amides, such as lithium amide catalysts, in general, and lithium hexamethyldisilazide, in particular, are preferred. The solvent for the selective silylation reaction is preferably an ethereal solvent such as tetrahydrofuran. Alternatively, however, other solvents such as ether or dimethoxyethane may be used. The temperature at which the C(10) selective silylation is carried out is not narrowly critical. In general, however, it is carried out at 0 °C or greater.

Selective esterification of the C(7) hydroxyl group of a C(10) protected taxane can be achieved using any of a variety of common acylating agents including, but not limited to, substituted and unsubstituted carboxylic acid derivatives, e.g., carboxylic acid halides, anhydrides, dicarbonates, isocyanates and haloformates. For example, the C(7) hydroxyl group of the 10-protected-10-deacteyl baccatin III can be selectively acylated with dibenzyl dicarbonate, diallyl dicarbonate, 2,2,2-trichloroethyl chloroformate, benzyl chloroformate or another common acylating agent. In general, acylation of the C(7) hydroxy group of a C(10) protected taxane are more efficient and more selective than are C(7) acylations of a 7,10-dihydroxy taxane such as 10-DAB; stated another way, once the C(10) hydroxyl group has been protected, there is a significant difference in the reactivity of the remaining C(7), C(13), and C(1) hydroxyl groups. These acylation reactions may optionally be carried out in the presence or absence of an amine base.

Derivatives of 10-deacetylbaccatin III having alternative substituents at C(2), C(9) and C(14) and processes for their preparation are known in the art. Taxane derivatives having acyloxy substituents other than benzoyloxy at C(2) may be prepared, for example, as described in Holton et al., U.S. Patent No. 5,728,725 or Kingston et al., U.S. Patent No. 6,002,023. Taxanes having acyloxy or hydroxy substituents at C(9) in place of keto may be prepared, for example as described in Holton et al., U.S. Patent No. 6,011,056 or Gunawardana et al., U.S. Patent No. 5,352,806. Taxanes having a beta hydroxy substituent at C(14) may be prepared from naturally occurring 14-hydroxy-10-deacetylbaccatin III.

Processes for the preparation and resolution of the β-lactam starting material are generally well known. For example, the β-lactam may be prepared as described in Holton, U.S. Patent No. 5,430,160 and the resulting enatiomeric mixtures of β-lactams may be resolved by a stereoselective hydrolysis using a lipase or enzyme as described, for example, in Patel, U.S. Patent No. 5,879,929 Patel U.S. Patent No. 5,567,614 or a liver homogenate as described, for example, in PCT Patent Application No. 00/41204. In a preferred embodiment in which the β-lactam is furyl substituted at the C(4) position, the β-lactam can be prepared as illustrated in the following reaction scheme:



wherein Ac is acetyl, NEt_3 is triethylamine, CAN is ceric ammonium nitrate, and p-TsOH is p-toluenesulfonic acid. The beef liver resolution may be carried out, for example, by combining the enatiomeric β-lactam mixture with a beef liver suspension (prepared, for example, by adding 20 g of frozen beef liver to a blender and then adding a pH 8 buffer to make a total volume of 1 L).

Compounds of formula 1 of the instant invention are useful for inhibiting tumor growth in mammals including humans and are preferably administered in the form of a pharmaceutical composition comprising an effective antitumor amount of a compound of the instant invention in combination with at least one pharmaceutically or pharmacologically acceptable carrier. The carrier, also known in the art as an excipient, vehicle, auxiliary, adjuvant, or diluent, is any substance which is pharmaceutically inert, confers a suitable consistency or form to the composition, and does not diminish the therapeutic efficacy of the antitumor compounds. The carrier is "pharmaceutically or pharmacologically acceptable" if

it does not produce an adverse, allergic or other untoward reaction when administered to a mammal or human, as appropriate.

The pharmaceutical compositions containing the antitumor compounds of the present invention may be formulated in any conventional manner. Proper formulation is dependent upon the route of administration chosen. The compositions of the invention can be formulated for any route of administration so long as the target tissue is available via that route. Suitable routes of administration include, but are not limited to, oral, parenteral (e.g., intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intraperitoneal, or intrasternal), topical (nasal, transdermal, intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavital, vaginal, transurethral, intradermal, aural, intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopical, transmucosal, sublingual and intestinal administration.

Pharmaceutically acceptable carriers for use in the compositions of the present invention are well known to those of ordinary skill in the art and are selected based upon a number of factors: the particular antitumor compound used, and its concentration, stability and intended bioavailability; the disease, disorder or condition being treated with the composition; the subject, its age, size and general condition; and the route of administration. Suitable carriers are readily determined by one of ordinary skill in the art (see, for example, J. G. Nairn, in: Remington's Pharmaceutical Science (A. Gennaro, ed.), Mack Publishing Co., Easton, Pa., (1985), pp. 1492-1517, the contents of which are incorporated herein by reference).

The compositions are preferably formulated as tablets, dispersible powders, pills, capsules, gelcaps, caplets, gels, liposomes, granules, solutions, suspensions, emulsions, syrups, elixirs, troches, dragees, lozenges, or any other dosage form which can be administered orally. Techniques and compositions for making oral dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

The compositions of the invention for oral administration comprise an effective antitumor amount of a compound of the invention in a pharmaceutically acceptable carrier. Suitable carriers for solid dosage forms include sugars,

starches, and other conventional substances including lactose, talc, sucrose, gelatin, carboxymethylcellulose, agar, mannitol, sorbitol, calcium phosphate, calcium carbonate, sodium carbonate, kaolin, alginic acid, acacia, corn starch, potato starch, sodium saccharin, magnesium carbonate, tragacanth, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, and stearic acid. Further, such solid dosage forms may be uncoated or may be coated by known techniques; e.g., to delay disintegration and absorption.

The antitumor compounds of the present invention are also preferably formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intraperitoneal, or intrasternal routes. The compositions of the invention for parenteral administration comprise an effective antitumor amount of the antitumor compound in a pharmaceutically acceptable carrier. Dosage forms suitable for parenteral administration include solutions, suspensions, dispersions, emulsions or any other dosage form which can be administered parenterally. Techniques and compositions for making parenteral dosage forms are known in the art.

Suitable carriers used in formulating liquid dosage forms for oral or parenteral administration include nonaqueous, pharmaceutically-acceptable polar solvents such as oils, alcohols, amides, esters, ethers, ketones, hydrocarbons and mixtures thereof, as well as water, saline solutions, dextrose solutions (e.g., DW5), electrolyte solutions, or any other aqueous, pharmaceutically acceptable liquid.

Suitable nonaqueous, pharmaceutically-acceptable polar solvents include, but are not limited to, alcohols (e.g., α-glycerol formal, β-glycerol formal, 1, 3-butyleneglycol, aliphatic or aromatic alcohols having 2-30 carbon atoms such as methanol, ethanol, propanol, isopropanol, butanol, t-butanol, hexanol, octanol, amylene hydrate, benzyl alcohol, glycerin (glycerol), glycol, hexylene glycol, tetrahydrofurfuryl alcohol, lauryl alcohol, cetyl alcohol, or stearyl alcohol, fatty acid esters of fatty alcohols such as polyalkylene glycols (e.g., polypropylene glycol, polyethylene glycol), sorbitan, sucrose and cholesterol); amides (e.g., dimethylacetamide (DMA), benzyl benzoate DMA, dimethylformamide, N-(β-hydroxyethyl)-lactamide, N, N-dimethylacetamide_amides, 2-pyrrolidinone, 1-methyl-2-pyrrolidinone, or polyvinylpyrrolidone); esters (e.g., 1-methyl-2-pyrrolidinone, 2-pyrrolidinone, acetate esters such as monoacetin, diacetin, and

triacetin, aliphatic or aromatic esters such as ethyl caprylate or octanoate, alkyl oleate, benzyl benzoate, benzyl acetate, dimethylsulfoxide (DMSO), esters of glycerin such as mono, di, or tri-glyceryl citrates or tartrates, ethyl benzoate, ethyl acetate, ethyl carbonate, ethyl lactate, ethyl oleate, fatty acid esters of sorbitan, fatty acid derived PEG esters, glyceryl monostearate, glyceride esters such as mono, di, or tri-glycerides, fatty acid esters such as isopropyl myristrate, fatty acid derived PEG esters such as PEG-hydroxyoleate and PEG-hydroxystearate, N-methyl pyrrolidinone, pluronic 60, polyoxyethylene sorbitol oleic polyesters such as poly(ethoxylated)$_{30-60}$ sorbitol poly(oleate)$_{2-4,}$ poly(oxyethylene)$_{15-20}$ monooleate, poly(oxyethylene)$_{15-20}$ mono 12-hydroxystearate, and poly(oxyethylene)$_{15-20}$ mono ricinoleate, polyoxyethylene sorbitan esters such as polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate, polyoxyethylene-sorbitan monostearate, and Polysorbate® 20, 40, 60 or 80 from ICI Americas, Wilmington, DE, polyvinylpyrrolidone, alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., Cremophor® EL solution or Cremophor® RH 40 solution), saccharide fatty acid esters (i.e., the condensation product of a monosaccharide (e.g., pentoses such as ribose, ribulose, arabinose, xylose, lyxose and xylulose, hexoses such as glucose, fructose, galactose, mannose and sorbose, trioses, tetroses, heptoses, and octoses), disaccharide (e.g., sucrose, maltose, lactose and trehalose) or oligosaccharide or mixture thereof with a C_4-C_{22} fatty acid(s)(e.g., saturated fatty acids such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid and stearic acid, and unsaturated fatty acids such as palmitoleic acid, oleic acid, elaidic acid, erucic acid and linoleic acid)), or steroidal esters); alkyl, aryl, or cyclic ethers having 2-30 carbon atoms (e.g., diethyl ether, tetrahydrofuran, dimethyl isosorbide, diethylene glycol monoethyl ether); glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether); ketones having 3-30 carbon atoms (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone); aliphatic, cycloaliphatic or aromatic hydrocarbons having 4-30 carbon atoms (e.g., benzene, cyclohexane, dichloromethane, dioxolanes, hexane, n-decane, n-dodecane, n-hexane, sulfolane, tetramethylenesulfon, tetramethylenesulfoxide, toluene, dimethylsulfoxide (DMSO), or tetramethylenesulfoxide); oils of mineral, vegetable, animal, essential or synthetic origin (e.g., mineral oils such as aliphatic or wax-based hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic based hydrocarbons, and refined paraffin oil, vegetable oils such as linseed, tung, safflower, soybean, castor,

cottonseed, groundnut, rapeseed, coconut, palm, olive, corn, corn germ, sesame, persic and peanut oil and glycerides such as mono-, di- or triglycerides, animal oils such as fish, marine, sperm, cod-liver, haliver, squalene, squalane, and shark liver oil, oleic oils, and polyoxyethylated castor oil); alkyl or aryl halides having 1-30 carbon atoms and optionally more than one halogen substituent; methylene chloride; monoethanolamine; petroleum benzin; trolamine; omega-3 polyunsaturated fatty acids (e.g., alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid); polyglycol ester of 12-hydroxystearic acid and polyethylene glycol (Solutol® HS-15, from BASF, Ludwigshafen, Germany); polyoxyethylene glycerol; sodium laurate; sodium oleate; or sorbitan monooleate.

Other pharmaceutically acceptable solvents for use in the invention are well known to those of ordinary skill in the art, and are identified in The Chemotherapy Source Book (Williams & Wilkens Publishing), The Handbook of Pharmaceutical Excipients, (American Pharmaceutical Association, Washington, D.C., and The Pharmaceutical Society of Great Britain, London, England, 1968), Modern Pharmaceutics, (G. Banker et al., eds., 3d ed.)(Marcel Dekker, Inc., New York, New York, 1995), The Pharmacological Basis of Therapeutics, (Goodman & Gilman, McGraw Hill Publishing), Pharmaceutical Dosage Forms, (H. Lieberman et al., eds.,)(Marcel Dekker, Inc., New York, New York, 1980), Remington's Pharmaceutical Sciences (A. Gennaro, ed., 19th ed.)(Mack Publishing, Easton, PA, 1995), The United States Pharmacopeia 24, The National Formulary 19, (National Publishing, Philadelphia, PA, 2000), A.J. Spiegel et al., and Use of Nonaqueous Solvents in Parenteral Products, JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 52, No. 10, pp. 917-927 (1963).

Preferred solvents include those known to stabilize the antitumor compounds, such as oils rich in triglycerides, for example, safflower oil, soybean oil or mixtures thereof, and alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., Cremophor® EL solution or Cremophor® RH 40 solution). Commercially available triglycerides include Intralipid® emulsified soybean oil (Kabi-Pharmacia Inc., Stockholm, Sweden), Nutralipid ® emulsion (McGaw, Irvine, California), Liposyn® II 20% emulsion (a 20% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, Illinois), Liposyn® III 2% emulsion (a 2% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg

phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, Illinois), natural or synthetic glycerol derivatives containing the docosahexaenoyl group at levels between 25% and 100% by weight based on the total fatty acid content (Dhasco® (from Martek Biosciences Corp., Columbia, MD), DHA Maguro® (from Daito Enterprises, Los Angeles, CA), Soyacal®, and Travemulsion®. Ethanol is a preferred solvent for use in dissolving the antitumor compound to form solutions, emulsions, and the like.

Additional minor components can be included in the compositions of the invention for a variety of purposes well known in the pharmaceutical industry. These components will for the most part impart properties which enhance retention of the antitumor compound at the site of administration, protect the stability of the composition, control the pH, facilitate processing of the antitumor compound into pharmaceutical formulations, and the like. Preferably, each of these components is individually present in less than about 15 weight % of the total composition, more preferably less than about 5 weight %, and most preferably less than about 0.5 weight % of the total composition. Some components, such as fillers or diluents, can constitute up to 90 wt.% of the total composition, as is well known in the formulation art. Such additives include cryoprotective agents for preventing reprecipitation of the taxane, surface active, wetting or emulsifying agents (e.g., lecithin, polysorbate-80, Tween® 80, pluronic 60, polyoxyethylene stearate), preservatives (e.g., ethyl-p-hydroxybenzoate), microbial preservatives (e.g., benzyl alcohol, phenol, m-cresol, chlorobutanol, sorbic acid, thimerosal and paraben), agents for adjusting pH or buffering agents (e.g., acids, bases, sodium acetate, sorbitan monolaurate), agents for adjusting osmolarity (e.g., glycerin), thickeners (e.g., aluminum monostearate, stearic acid, cetyl alcohol, stearyl alcohol, guar gum, methyl cellulose, hydroxypropylcellulose, tristearin, cetyl wax esters, polyethylene glycol), colorants, dyes, flow aids, non-volatile silicones (e.g., cyclomethicone), clays (e.g., bentonites), adhesives, bulking agents, flavorings, sweeteners, adsorbents, fillers (e.g., sugars such as lactose, sucrose, mannitol, or sorbitol, cellulose, or calcium phosphate), diluents (e.g., water, saline, electrolyte solutions), binders (e.g., starches such as maize starch, wheat starch, rice starch, or potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, sugars, polymers, acacia), disintegrating agents (e.g., starches such as maize starch, wheat starch, rice starch, potato starch, or carboxymethyl starch, cross-linked polyvinyl pyrrolidone, agar, alginic acid or a

salt thereof such as sodium alginate, croscarmellose sodium or crospovidone), lubricants (e.g., silica, talc, stearic acid or salts thereof such as magnesium stearate, or polyethylene glycol), coating agents (e.g., concentrated sugar solutions including gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, or titanium dioxide), and antioxidants (e.g., sodium metabisulfite, sodium bisulfite, sodium sulfite, dextrose, phenols, and thiophenols).

In a preferred embodiment, a pharmaceutical composition of the invention comprises at least one nonaqueous, pharmaceutically acceptable solvent and an antitumor compound having a solubility in ethanol of at least about 100, 200, 300, 400, 500, 600, 700 or 800 mg/ml. While not being bound to a particular theory, it is believed that the ethanol solubility of the antitumor compound may be directly related to its efficacy. The antitumor compound can also be capable of being crystallized from a solution. In other words, a crystalline antitumor compound, such as compound 1393, can be dissolved in a solvent to form a solution and then recrystallized upon evaporation of the solvent without the formation of any amorphous antitumor compound. It is also preferred that the antitumor compound have an ID50 value (i.e, the drug concentration producing 50% inhibition of colony formation) of at least 4, 5, 6, 7, 8, 9, or 10 times less that of paclitaxel when measured according to the protocol set forth in the working examples.

Dosage form administration by these routes may be continuous or intermittent, depending, for example, upon the patient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to and assessable by a skilled practitioner.

Dosage and regimens for the administration of the pharmaceutical compositions of the invention can be readily determined by those with ordinary skill in treating cancer. It is understood that the dosage of the antitumor compounds will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. For any mode of administration, the actual amount of antitumor compound delivered, as well as the dosing schedule necessary to achieve the advantageous effects described herein, will also depend, in part, on such factors as the bioavailability of the antitumor compound, the disorder being treated, the desired therapeutic dose, and other factors that will be apparent to those of skill in the art. The dose administered to an animal, particularly a

human, in the context of the present invention should be sufficient to effect the desired therapeutic response in the animal over a reasonable period of time. Preferably, an effective amount of the antitumor compound, whether administered orally or by another route, is any amount which would result in a desired therapeutic response when administered by that route. Preferably, the compositions for oral administration are prepared in such a way that a single dose in one or more oral preparations contains at least 20 mg of the antitumor compound per m^2 of patient body surface area, or at least 50, 100, 150, 200, 300, 400, or 500 mg of the antitumor compound per m^2 of patient body surface area, wherein the average body surface area for a human is 1.8 m^2. Preferably, a single dose of a composition for oral administration contains from about 20 to about 600 mg of the antitumor compound per m^2 of patient body surface area, more preferably from about 25 to about 400 $mg/m^{2,}$ even more preferably, from about 40 to about 300 mg/m^2, and even more preferably from about 50 to about 200 mg/m^2. Preferably, the compositions for parenteral administration are prepared in such a way that a single dose contains at least 20 mg of the antitumor compound per m^2 of patient body surface area, or at least 40, 50, 100, 150, 200, 300, 400, or 500 mg of the antitumor compound per m^2 of patient body surface area. Preferably, a single dose in one or more parenteral preparations contains from about 20 to about 500 mg of the antitumor compound per m^2 of patient body surface area, more preferably from about 40 to about 400 $mg/m^{2,}$ and even more preferably, from about 60 to about 350 mg/m^2. However, the dosage may vary depending on the dosing schedule which can be adjusted as necessary to achieve the desired therapeutic effect. It should be noted that the ranges of effective doses provided herein are not intended to limit the invention and represent preferred dose ranges. The most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of ordinary skill in the art without undue experimentation.

The concentration of the antitumor compound in a liquid pharmaceutical composition is preferably between about 0.01 mg and about 10 mg per ml of the composition, more preferably between about 0.1 mg and about 7 mg per ml, even more preferably between about 0.5 mg and about 5 mg per ml, and most preferably between about 1.5 mg and about 4 mg per ml. Relatively low concentrations are generally preferred because the antitumor compound is most soluble in the solution at low concentrations. The concentration of the antitumor compound in a solid pharmaceutical composition for oral administration is

preferably between about 5 weight % and about 50 weight %, based on the total weight of the composition, more preferably between about 8 weight % and about 40 weight %, and most preferably between about 10 weight % and about 30 weight %.

In one embodiment, solutions for oral administration are prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is a solution, such as Cremophor® EL solution, is added to the solution while stirring to form a pharmaceutically acceptable solution for oral administration to a patient. If desired, such solutions can be formulated to contain a minimal amount of, or to be free of, ethanol, which is known in the art to cause adverse physiological effects when administered at certain concentrations in oral formulations.

In another embodiment, powders or tablets for oral administration are prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g.,ethanol or methylene chloride) to form a solution. The solvent can optionally be capable of evaporating when the solution is dried under vacuum. An additional carrier can be added to the solution prior to drying, such as Cremophor® EL solution. The resulting solution is dried under vacuum to form a glass. The glass is then mixed with a binder to form a powder. The powder can be mixed with fillers or other conventional tabletting agents and processed to form a tablet for oral administration to a patient. The powder can also be added to any liquid carrier as described above to form a solution, emulsion, suspension or the like for oral administration.

Emulsions for parenteral administration can be prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is an emulsion, such as Liposyn® II or Liposyn® III emulsion, is added to the solution while stirring to form a pharmaceutically acceptable emulsion for parenteral administration to a patient. If desired, such emulsions can be formulated to contain a minimal amount of, or to be free of, ethanol or Cremophor® solution, which are known in the art to cause adverse physiological effects when administered at certain concentrations in parenteral formulations.

Solutions for parenteral administration can be prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is a solution, such as Cremophor® solution, is added to the solution while stirring to form a pharmaceutically acceptable solution for parenteral administration to a patient. If desired, such solutions can be formulated to contain a minimal amount of, or to be free of, ethanol or Cremophor® solution, which are known in the art to cause adverse physiological effects when administered at certain concentrations in parenteral formulations.

If desired, the emulsions or solutions described above for oral or parenteral administration can be packaged in IV bags, vials or other conventional containers in concentrated form and diluted with any pharmaceutically acceptable liquid, such as saline, to form an acceptable taxane concentration prior to use as is known in the art.

<u>Definitions</u>

The terms "hydrocarbon" and “hydrocarbyl” as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

The “substituted hydrocarbyl” moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term “heteroatom” shall mean atoms other than carbon and hydrogen.

The “heterosubstituted methyl” moieties described herein are methyl groups in which the carbon atom is covalently bonded to at least one heteroatom and optionally with hydrogen, the heteroatom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom

may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, acyloxy, nitro, amino, amido, thiol, ketals, acetals, esters or ether moiety.

The "heterosubstituted acetate" moieties described herein are acetate groups in which the carbon of the methyl group is covalently bonded to at least one heteroatom and optionally with hydrogen, the heteroatom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, acyloxy, nitro, amino, amido, thiol, ketals, acetals, esters or ether moiety.

Unless otherwise indicated, the alkyl groups described herein are preferably lower alkyl containing from one to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like.

Unless otherwise indicated, the alkenyl groups described herein are preferably lower alkenyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

Unless otherwise indicated, the alkynyl groups described herein are preferably lower alkynyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

The terms "aryl" or "ar" as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl.

The terms "halogen" or "halo" as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or nonaromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the

molecule through a carbon or heteroatom. Exemplary heterocyclo include heteroaromatics such as furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "heteroaromatic" as used herein alone or as part of another group denote optionally substituted aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heteroaromatic group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heteroaromatics include furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "acyl," as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxyl group from the group --COOH of an organic carboxylic acid, e.g., RC(O)-, wherein R is R^1, R^1O-, R^1R^2N-, or R^1S-, R^1 is hydrocarbyl, heterosubstituted hydrocarbyl, or heterocyclo, and R^2 is hydrogen, hydrocarbyl or substituted hydrocarbyl.

The term "acyloxy," as used herein alone or as part of another group, denotes an acyl group as described above bonded through an oxygen linkage (--O--), e.g., RC(O)O- wherein R is as defined in connection with the term "acyl."

Unless otherwise indicated, the alkoxycarbonyloxy moieties described herein comprise lower hydrocarbon or substituted hydrocarbon or substituted hydrocarbon moieties.

Unless otherwise indicated, the carbamoyloxy moieties described herein are derivatives of carbamic acid in which one or both of the amine hydrogens is optionally replaced by a hydrocarbyl, substituted hydrocarbyl or heterocyclo moiety.

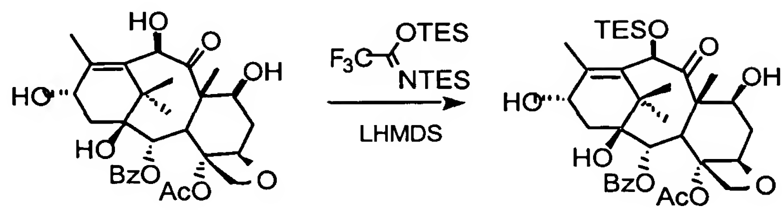
The terms "hydroxyl protecting group" and "hydroxy protecting group" as used herein denote a group capable of protecting a free hydroxyl group ("protected hydroxyl") which, subsequent to the reaction for which protection is employed, may be removed without disturbing the remainder of the molecule. A

variety of protecting groups for the hydroxyl group and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981, or Fieser & Fieser. Exemplary hydroxyl protecting groups include methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, (.beta.-trimethylsilylethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxycarbonyl, t-butyl(diphenyl)silyl, trialkylsilyl, trichloromethoxycarbonyl and 2,2,2-trichloroethoxymethyl.

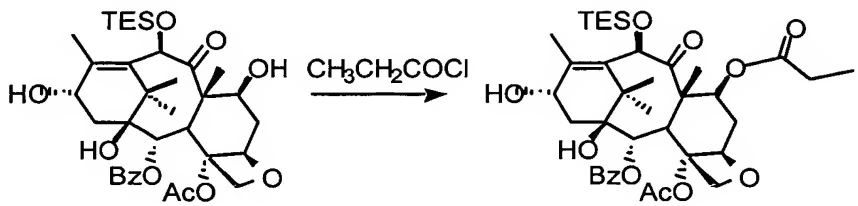
As used herein, "Ac" means acetyl; "Bz" means benzoyl; "Et" means ethyl; "Me" means methyl; "Ph" means phenyl; "Pr" means propyl; "Bu" means butyl; "Am" means amyl; "cpro" means cyclopropyl; "iPr" means isopropyl; "tBu" and "t-Bu" means tert-butyl; "R" means lower alkyl unless otherwise defined; "Py" means pyridine or pyridyl; "TES" means triethylsilyl; "TMS" means trimethylsilyl; "LAH" means lithium aluminum hydride; "10-DAB" means 10-desacetylbaccatin III"; "amine protecting group" includes, but is not limited to, carbamates, for example, 2,2,2-trichloroethylcarbamate or tertbutylcarbamate; "protected hydroxy" means -OP wherein P is a hydroxy protecting group; "PhCO" means phenylcarbonyl; "tBuOCO" and "Boc" mean tert-butoxycarbonyl; "tAmOCO" means tert-amyloxycarbonyl; "2-FuCO" means 2-furylcarbonyl; "2-ThCO" means 2-thienylcarbonyl; "2-PyCO" means 2-pyridylcarbonyl; "3-PyCO" means 3-pyridylcarbonyl; "4-PyCO" means 4-pyridylcarbonyl; "C_4H_7CO" means butenylcarbonyl; "tC_3H_5CO" means *trans*-propenylcarbonyl; "EtOCO" means ethoxycarbonyl; "ibueCO" means isobutenylcarbonyl; "iBuCO" means isobutylcarbonyl; "iBuOCO" means isobutoxycarbonyl; "iPrOCO" means isopropyloxycarbonyl; "nPrOCO" means n-propyloxycarbonyl; "nPrCO" means n-propylcarbonyl; "ibue" means isobutenyl; "THF" means tetrahydrofuran; "DMAP" means 4-dimethylamino pyridine; "LHMDS" means Lithium HexamethylDiSilazanide.

The following examples illustrate the invention.

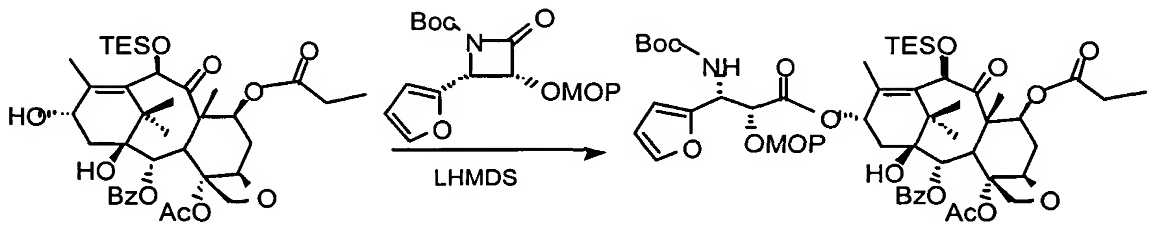
Example 1



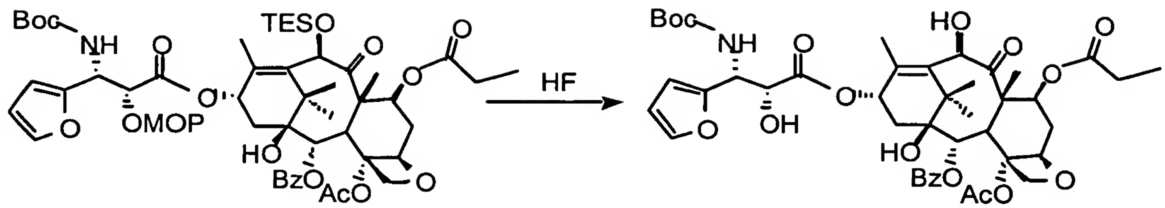
10-Triethylsilyl-10-deacetyl baccatin III. To a solution of 1.0 g (1.84 mmol) of 10-deacetyl baccatin III in 50 mL of THF at -10 °C under a nitrogen atmosphere was added 0.857 mL (2.76 mmol, 1.5 mol equiv) of *N,O*-(bis)-TES-trifluoroacetamide over a period of 3 min. This was followed by the addition of 0.062 mL of a 0.89 M THF solution of lithium bis(trimethylsilyl)amide (0.055 mmol, 0.03 mol equiv). After 10 min 0.038 mL (0.92 mmol, 0.5 mol equiv) of methanol was added, and after an additional 5 min 4 mL (0.055 mmol, 0.03 mol equiv) of acetic acid was added. The solution was diluted with 300 mL of ethyl acetate and washed two times with 100 mL of saturated aqueous sodium bicarbonate solution. The combined aqueous layers were extracted with 100 mL of ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. To the residue was added 100 mL of hexane and the solid (1.23 g, 101%) was collected by filtration. Recrystallization of the solid by dissolving in boiling ethyl acetate (20 mL, 17 mL/g) and cooling to room temperature gave 1.132 g (94%) of a white solid. m.p. 242 °C; $[\alpha]_D^{25}$ -60.4 (c 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz) δ (p.p.m): 8.10 (2H, d, *Jm* = 7.5Hz, Bz*o*), 7.60 (1H, t, *Jm* = 7.5Hz, Bz*p*), 7.47 (2H, t, *Jo* = 7.5Hz, Bz*m*), 5.64 (1H, d, *J3* = 6.9Hz, H2), 5.26 (1H, s, H10), 4.97 (1H, dd, *J6β* = 2.2Hz, *J6α* = 9.9Hz, H5), 4.85 (1H, dd, *J14α* = 8.9Hz, *J14β* = 8.9Hz, H13), 4.30 (1H, d, *J20β* = 8.5Hz, H20α), 4.23 (1H, ddd, *J7OH* = 4.5Hz, *J6α* = 6.6Hz, *J6β* = 11.0Hz, H7), 4.15 (1H, d, *J20α* = 8.5Hz, H20β), 4.00 (1H, d, *J2* = 6.9Hz, H3), 2.58 (1H, ddd, *J7* = 6.6Hz, *J5* = 9.9Hz, *J6β* = 14.5Hz, H6α), 2.28-2.25 (5H, m, 4Ac, H14α, H14β), 2.02 (3H, s, 18Me), 1.97 (1H, d, *J7* = 4.5Hz, H7OH), 1.78 (1H, ddd, *J7* = 11.0Hz, *J5* = 2.2Hz, *J6α* = 14.5Hz, H6β), 1.68 (3H, s, 19Me), 1.56 (1H, s, OH1), 1.32 (1H, d, *J13* = 8.8Hz, OH13), 1.18 (3H, s, 17Me), 1.06 (3H, s, 16Me), 0.98 (9H, t, JCH_2(TES) = 7.3Hz, CH_3(TES)), 0.65 (6H, dq, JCH_3(TES) = 7.3Hz, CH_2(TES)).



10-Triethylsilyl-10-deacetyl-7-propionyl baccatin III. To a solution of 1.0 g (1.517 mmol) of 10-triethylsilyl-10-deacetyl baccatin III and 37.0 mg (0.303 mmol) of DMAP in 20 mL of dichloromethane at room temperature under a nitrogen atmosphere was added 0.920 mL (11.381 mmol) of pyridine and 0.329 mL (3.794 mmol, 2.5 mol equiv) of propionyl chloride in that order. The mixture was stirred at room temperature for 6 h, diluted with 350 mL of ethyl acetate and extracted with 50 mL of 10% aqueous copper sulfate solution. The organic layer was washed with 50 mL of saturated aqueous sodium bicarbonate solution, 50 mL of brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product was dissolved in 75 mL of ethyl acetate, 100 mg of Norit A was added, the mixture was filtered through celite and concentrated under reduced pressure to give 1.13 g of material. Recrystallization from ethyl acetate/hexanes (dissolved in 6.5 mL of refluxing ethyl acetate, then 24 mL of hexanes added, allowed to cool to room temperature, and left to stand for 17 h) afforded 787 mg (72.5%) of a white crystalline solid. A second recrystallization (*ca* 340 mg material dissolved in 2 mL of refluxing ethyl acetate, then 10 mL of hexanes added, allowed to cool to room temperature, and allowed to stand for 17 h) afforded 181 mg (16.7 %) of a white crystalline solid. The combined yield after recrystallization was 89.2%. m.p. 129 °C; $[\alpha]_D^{25}$ -47.9 (c 1.0, $CHCl_3$); NMR ^1H ($CDCl_3$, 300MHz) δ (ppm): 8.10 (2H, d, *Jm* = 7.4Hz, Bz*o*), 7.60 (1H, t, *Jm* = 7.4Hz, Bz*p*), 7.48 (2H, dd, *Jo* = 7.4Hz, *Jp* = 7.4Hz, Bz*m*), 5.64 (1H, d, *J3* = 7.4Hz, H2), 5.47 (1H, dd, *J6*α = 7.4Hz, *J6*β = 10.1Hz, H7), 5.28 (1H, s, H10), 4.94 (1H, d, *J6*α = 9.4Hz, H5), 4.80 - 4.90 (1H, m, H13), 4.31 (1H, d, *J20*β = 8.1Hz, H20α), 4.16 (1H, d, *J20*α = 8.1Hz, H20β), 4.06 (1H, d, *J2* = 7.4Hz, H3), 2.55 (1H, ddd, *J7* = 7.4Hz, *J5* = 9.4Hz, *J6*β = 14.8Hz, H6α), 2.28 (3H, s, 4Ac), 2.23 - 2.32 (4H, m, 7CH2, H14α, H14β), 2.07 (3H, s, 18Me), 2.02 (1H, d, *J13* = 4.7Hz, OH13), 1.76 - 1.87 (4H, m, H6β, 19Me), 1.60 (1H, s, OH1), 1.17 (3H, s, 17Me), 1.09 (3H, t, *J* $7CH_2$ = 7.4Hz, $7CH_3$), 1.04 (3H, s, 16Me), 0.96 (9H, t, JCH_2(TES) = 8.0Hz, CH_3(TES)), 0.52 - 0.62 (6H, m, CH_2(TES)).



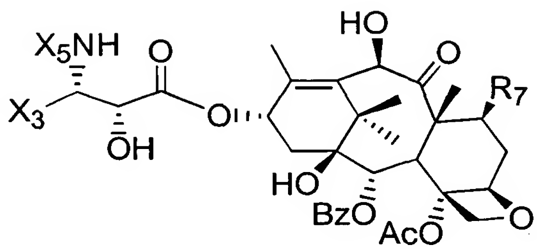
2'-O-MOP-3'-desphenyl-3'-(2-furyl)-10-triethylsilyl-7-propionyl taxotere. To a solution of 493 mg (0.690 mmol) of 10-triethylsilyl-10-deacetyl-7-propionyl baccatin III in 4 mL of anhydrous THF under a nitrogen atmosphere at -45 °C was added 0.72 mL (0.72 mmol) of a 1M solution of LiHMDS in THF. After 0.5 h a solution of 263 mg (0.814 mmol) of the b-Lactam (predried as described above) in 2 mL of anhydrous THF was added. The mixture was warmed to 0 °C, and after 2 h 0.5 mL of saturated aqueous sodium bicarbonate solution was added. The mixture was diluted with 50 ml of ethyl acetate and washed two times with 5 mL of brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure to give 742 mg (104%) of a slightly yellow solid. The solid was recrystallized by dissolving it in 12 mL of a 1:5 mixture of ethyl acetate and hexane at reflux and then cooling to room temperature to give 627 mg (88%) of a white crystalline solid. Evaporation of the mother liquor gave 96 mg of material which was recrystallized as above from 2 mL of a 1:5 mixture of ethyl acetate and hexane to give an additional 46 mg (6%) of white crystalline solid. The total yield from recrystallization was 94%. Evaporation of the mother liquor gave 46 mg of material which was purified by column chromatography on silica gel to give an additional 20 mg (3%) of product. m.p. 207-209 °C; $[a]_D^{25}$ -30.0 (c 5.0, methanol); ^{1}H NMR ($CDCl_3$, 400MHz) d (ppm): 8.09-8.11 (m, 2H), 7.58-7.61 (m, 1H), 7.47-7.51(m, 2H), 7.39 (d, J = 0.8 Hz, 1H), 6.34 (dd, J = 3.2, 1.6 Hz, 1H), 6.26 (d, J = 3.2 Hz), 6.14 (dd, J = 8.8, 8.8 Hz, 1H), 5.71 (d, J = 6.8 Hz, 1H), 5.47 (dd, J = 10.0, 7.2 Hz, 1H), 5.30-5.36 (m, 2H), 5.28 (s, 1H), 4.95 (d, J = 7.6 Hz, 1H), 4.76 (s, 1H), 4.33 (d, J= 8.0 Hz, 1H), 4,19 (d, J = 8.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 1H), 2.83 (s, 3H), 2.55 (ddd, J = 17.2, 9.6, 7.6, 1H), 2.50 (s, 3H), 2.20-2.40 (m, 2H), 2.28 (q, J = 7.6 Hz, 2H), 1.95 (s, 3H), 1.84 (ddd, J = 14.8, 10.8, 2 Hz), 1.80 (s, 3H), 1.67 (s, 1H), 1.39 (s, 9H), 1.32 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.74 (s, 3H), 1.09 (t, J = 7.6 Hz, 3H), 0.93-0.99 (m, 9H), 0.50-0.65 (m, 6H).



3'-Desphenyl-3'-(2-furyl)-7-propionyl taxotere. (1393) To a solution of 206 mg (0.199 mmol) of 2'-O-MOP-3'-desphenyl-3'-(2-furyl)-10-triethylsilyl-7-propionyl taxotere in 1.7 mL of pyridine and 5.4 mL of acetonitrile at 0 °C was added 0.80 mL (2.0 mmol) of an aqueous solution containing 49% HF. The mixture was warmed to room temperature for 14 h and was then diluted with 20 mL of ethyl acetate and washed three times with 2 mL of saturated aqueous sodium bicarbonate and then with 8 mL of brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure to give 170 mg (100%) of a white solid. The crude product was crystallized with 2 mL of solvent (CH_2Cl_2:hexane=1:1.7) to give 155 mg (90.5%) of white crystals. Concentration of the mother liquor under reduced pressure gave 15 mg of material which was recrystallized using 0.2 mL of a 1:1.7 mixture of methylene chloride and hexane to give an additional 11 mg (7.5%) of white crystals. The total yield from recrystallization was 98%. m.p. 150-152 °C; $[a]_D^{25}$ -27.0 (c 5.0, methanol); Anal. Calcd for $C_{44}H_{55}NO_{16}$•$0.5H_2O$: C, 61.18; H, 6.48. Found: C, 61.40; H, 6.65. ^1H NMR ($CDCl_3$, 500 MHz) d (ppm): 8.11 (d, J = 7.5 Hz, 2H), 7.61 (dd, J = 7.5, 7.5 Hz, 1H), 7.50 (dd, J = 8.0, 7.5 Hz 2H), 7.41 (d, J = 1.0 Hz, 1H), 6.38 (dd, J = 3.0, 2.0 Hz, 1H), 6.33 (d, J = 3.5 Hz), 6.22 (dd, J = 9.5, 9.5 Hz, 1H), 5.69 (d, J = 7.0 Hz, 1H), 5.49 (dd, J = 11.0, 7.5 Hz, 1H), 5.35 (d, J = 9.5 Hz, 1H), 5.33 (d, J = 1.5 Hz, 1H), 5.25 (d, J = 9.5 Hz, 1H), 4.94 (d, J = 8.5 Hz, 1H), 4.71 (dd, J = 5.5, 2.0 Hz, 1H), 4.33 (d, J= 8.5 Hz, 1H), 4,21 (d, J = 8.5 Hz, 1H), 4.01 (d, J = 6.5 Hz, 1H), 3.97 (d, J = 1.5 Hz, 1H), 3.30 (d, J = 5.5 Hz, 1H), 2.54 (ddd, J = 16.5, 9.5, 7.0, 1H), 2.41 (s, 3H), 2.37 (dd, J = 15.0, 9.0 Hz, 1H), 2.30 (dd, J = 17.5, 9.5 Hz, 1H), 2.25 (q, J = 7.5 Hz, 2H), 1.96 (s, 3H), 1.93 (ddd, J = 14.5, 11.0, 2.5 Hz), 1.85 (s, 3H), 1.64 (s, 1H), 1.36 (s, 9H), 1.23 (s, 3H), 1.10 (t, J = 7.5 Hz, 3H).

Example 2

The procedures described in Example 1 were repeated, but other suitably protected β-lactams were substituted for the β-lactam of Example 1 to prepare the series of compounds having structural formula (13) and the combinations of substituents identified in the following table.



(13)

Compound	X_5	X_3	R_7
1351	tBuOCO-	ibue	EtCOO-
1364	tBuOCO-	2-pyridyl	EtCOO-
1372	tBuOCO-	3-pyridyl	EtCOO-
1386	tBuOCO-	4-pyridyl	EtCOO-
1393	tBuOCO-	2-furyl	EtCOO-
1401	tBuOCO-	3-furyl	EtCOO-
1418	tBuOCO-	2-thienyl	EtCOO-
1424	tBuOCO-	3-thienyl	EtCOO-
1434	tBuOCO-	isopropyl	EtCOO-
1447	tBuOCO-	cyclobutyl	EtCOO-
1458	tBuOCO-	phenyl	EtCOO-
3069	2-FuCO-	2-thienyl	EtCOO-
3082	iPrOCO-	2-thienyl	EtCOO-
3171	nPrCO-	2-furyl	EtCOO-
3196	iBuOCO-	2-furyl	EtCOO-
3232	iBuOCO-	2-thienyl	EtCOO-
3327	nPrCO-	2-thienyl	EtCOO-
3388	PhCO-	3-thienyl	EtCOO-
3444	iPrOCO-	2-furyl	EtCOO-
3479	2-ThCO-	2-thienyl	EtCOO-
3555	C_4H_7CO-	2-thienyl	EtCOO-
3560	tC_3H_5CO-	2-thienyl	EtCOO-

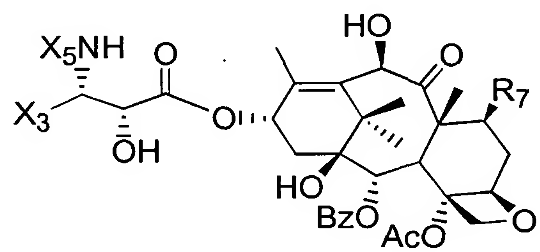
3611	EtOCO-	2-furyl	EtCOO-
3629	2-FuCO-	2-furyl	EtCOO-
3632	2-ThCO-	2-furyl	EtCOO-
3708	tC_3H_5CO-	2-furyl	EtCOO-
3713	C_4H_7CO-	2-furyl	EtCOO-
4017	PhCO-	2-furyl	EtCOO-
4044	EtOCO-	2-thienyl	EtCOO-
4106	3-PyCO-	2-thienyl	EtCOO-
4135	iPrOCO-	2-thienyl	PrCOO-
4175	PhCO-	2-thienyl	PrCOO-
4219	2-FuCO-	2-thienyl	PrCOO-
4256	tBuOCO-	2-thienyl	PrCOO-
4283	ibueCO-	2-thienyl	PrCOO-
4290	ibuOCO-	2-thienyl	PrCOO-
4312	ibueCO-	2-thienyl	EtCOO-
4388	2-ThCO-	2-thienyl	PrCOO-
4394	tBuOCO-	3-furyl	PrCOO-
4406	tBuOCO-	isobutenyl	PrCOO-
4446	tBuOCO-	3-thienyl	PrCOO-
4499	tBuOCO-	2-furyl	PrCOO-
4544	iBuOCO-	3-thienyl	EtCOO-
4600	iBuOCO-	3-thienyl	PrCOO-
4616	iBuOCO-	2-furyl	PrCOO-
4737	tC_3H_5CO-	2-furyl	PrCOO-
4757	tC_3H_5CO-	2-thienyl	PrCOO-
6171	ibueOCO-	2-furyl	EtCOO-
6131	ibueOCO-	2-furyl	iBuCOO-
5989	ibueOCO-	2-furyl	iPrCOO-
6141	ibueOCO-	2-furyl	nBuCOO-
6181	ibueOCO-	2-furyl	nPrCOO-
6040	ibuOCO-	2-furyl	ibueCOO-

6121	iPrCO-	2-furyl	iPrCOO-
6424	tAmOCO-	2-furyl	EtCOO-
6212	tAmOCO-	2-furyl	EtCOO-
6282	tAmOCO-	2-furyl	iBuCOO-
6252	tAmOCO-	2-furyl	iPrCOO-
6343	tAmOCO-	2-furyl	nBuCOO-
6272	tAmOCO-	2-furyl	nPrCOO-
6202	tC_3H_5CO-	2-furyl	iPrCOO-
4454	2-ThCO-	2-thienyl	nPrCOO-
4414	PhCO-	2-thienyl	nPrCOO-
6333	tBuOCO-	2-thienyl	iPrCOO-
6686	tBuOCO-	2-thienyl	tC_3H_5COO-
6363	tBuOCO-	2-thiazo	EtCOO-
4787	iBuOCO-	3-furyl	EtCOO-
4828	iBuOCO-	3-furyl	nPrCOO-
4898	tC_3H_5CO-	3-furyl	EtCOO-
4939	tC_3H_5CO-	3-furyl	nPrCOO-
5020	tC_3H_5CO-	3-thienyl	EtCOO-
5030	tC_3H_5CO-	3-thienyl	nPrCOO-
5191	iBuOCO-	cpro	EtCOO-
5202	iBuOCO-	cpro	nPrCOO-
5070	tBuOCO-	cpro	EtCOO-
5080	tBuOCO-	cpro	nPrCOO-
5121	iBuOCO-	ibue	EtCOO-
5131	iBuOCO-	ibue	nPrCOO-

Example 3

Following the processes described in Example 1 and elsewhere herein, the following specific taxanes having structural formula 14 may be prepared, wherein R_7 is as previously defined, including wherein R_7 is $R_{7a}COO$- and R_{7a} is (i) substituted or unsubstituted C_2 to C_8 alkyl (straight, branched or cyclic), such as ethyl, propyl, butyl, pentyl, or hexyl; (ii) substituted or unsubstituted C_2 to C_8

alkenyl (straight, branched or cyclic), such as ethenyl, propenyl, butenyl, pentenyl or hexenyl; (iii) substituted or unsubstituted C_2 to C_8 alkynyl (straight or branched) such as ethynyl, propynyl, butynyl, pentynyl, or hexynyl; (iv) substituted or unsubstituted phenyl; or (v) substituted or unsubstituted heterocyclo such as furyl, thienyl, or pyridyl. The substituents may be hydrocarbyl or any of the heteroatom containing substituents selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.



(14)

X_5	X_3	R_7
tBuOCO-	2-furyl	R_aCOO-
tBuOCO-	3-furyl	R_aCOO-
tBuOCO-	2-thienyl	R_aCOO-
tBuOCO-	3-thienyl	R_aCOO-
tBuOCO-	2-pyridyl	R_aCOO-
tBuOCO-	3-pyridyl	R_aCOO-
tBuOCO-	4-pyridyl	R_aCOO-
tBuOCO-	isobutenyl	R_aCOO-
tBuOCO-	isopropyl	R_aCOO-
tBuOCO-	cyclopropyl	R_aCOO-
tBuOCO-	cyclobutyl	R_aCOO-
tBuOCO-	cyclopentyl	R_aCOO-
tBuOCO-	phenyl	R_aCOO-
benzoyl	2-furyl	R_aCOO-
benzoyl	3-furyl	R_aCOO-

benzoyl	2-thienyl	R_aCOO-
benzoyl	3-thienyl	R_aCOO-
benzoyl	2-pyridyl	R_aCOO-
benzoyl	3-pyridyl	R_aCOO-
benzoyl	4-pyridyl	R_aCOO-
benzoyl	isobutenyl	R_aCOO-
benzoyl	isopropyl	R_aCOO-
benzoyl	cyclopropyl	R_aCOO-
benzoyl	cyclobutyl	R_aCOO-
benzoyl	cyclopentyl	R_aCOO-
benzoyl	phenyl	R_aCOO-
2-FuCO-	2-furyl	R_aCOO-
2-FuCO-	3-furyl	R_aCOO-
2-FuCO-	2-thienyl	R_aCOO-
2-FuCO-	3-thienyl	R_aCOO-
2-FuCO-	2-pyridyl	R_aCOO-
2-FuCO-	3-pyridyl	R_aCOO-
2-FuCO-	4-pyridyl	R_aCOO-
2-FuCO-	isobutenyl	R_aCOO-
2-FuCO-	isopropyl	R_aCOO-
2-FuCO-	cyclopropyl	R_aCOO-
2-FuCO-	cyclobutyl	R_aCOO-
2-FuCO-	cyclopentyl	R_aCOO-
2-FuCO-	phenyl	R_aCOO-
2-ThCO-	2-furyl	R_aCOO-
2-ThCO-	3-furyl	R_aCOO-
2-ThCO-	2-thienyl	R_aCOO-
2-ThCO-	3-thienyl	R_aCOO-
2-ThCO-	2-pyridyl	R_aCOO-
2-ThCO-	3-pyridyl	R_aCOO-
2-ThCO-	4-pyridyl	R_aCOO-

2-ThCO-	isobutenyl	R_aCOO-
2-ThCO-	isopropyl	R_aCOO-
2-ThCO-	cyclopropyl	R_aCOO-
2-ThCO-	cyclobutyl	R_aCOO-
2-ThCO-	cyclopentyl	R_aCOO-
2-ThCO-	phenyl	R_aCOO-
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3-PyCO-	4-pyridyl	R_aCOO-
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3-PyCO-	isopropyl	R_aCOO-
3-PyCO-	cyclopropyl	R_aCOO-
3-PyCO-	cyclobutyl	R_aCOO-
3-PyCO-	cyclopentyl	R_aCOO-

3-PyCO-	phenyl	R_aCOO-
4-PyCO-	2-furyl	R_aCOO-
4-PyCO-	3-furyl	R_aCOO-
4-PyCO-	2-thienyl	R_aCOO-
4-PyCO-	3-thienyl	R_aCOO-
4-PyCO-	2-pyridyl	R_aCOO-
4-PyCO-	3-pyridyl	R_aCOO-
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4-PyCO-	isopropyl	R_aCOO-
4-PyCO-	cyclopropyl	R_aCOO-
4-PyCO-	cyclobutyl	R_aCOO-
4-PyCO-	cyclopentyl	R_aCOO-
4-PyCO-	phenyl	R_aCOO-
C_4H_7CO-	2-furyl	R_aCOO-
C_4H_7CO-	3-furyl	R_aCOO-
C_4H_7CO-	2-thienyl	R_aCOO-
C_4H_7CO-	3-thienyl	R_aCOO-
C_4H_7CO-	2-pyridyl	R_aCOO-
C_4H_7CO-	3-pyridyl	R_aCOO-
C_4H_7CO-	4-pyridyl	R_aCOO-
C_4H_7CO-	isobutenyl	R_aCOO-
C_4H_7CO-	isopropyl	R_aCOO-
C_4H_7CO-	cyclopropyl	R_aCOO-
C_4H_7CO-	cyclobutyl	R_aCOO-
C_4H_7CO-	cyclopentyl	R_aCOO-
C_4H_7CO-	phenyl	R_aCOO-
EtOCO-	2-furyl	R_aCOO-
EtOCO-	3-furyl	R_aCOO-
EtOCO-	2-thienyl	R_aCOO-
EtOCO-	3-thienyl	R_aCOO-

EtOCO-	2-pyridyl	R_aCOO-
EtOCO-	3-pyridyl	R_aCOO-
EtOCO-	4-pyridyl	R_aCOO-
EtOCO-	isobutenyl	R_aCOO-
EtOCO-	isopropyl	R_aCOO-
EtOCO-	cyclopropyl	R_aCOO-
EtOCO-	cyclobutyl	R_aCOO-
EtOCO-	cyclopentyl	R_aCOO-
EtOCO-	phenyl	R_aCOO-
ibueCO-	2-furyl	R_aCOO-
ibueCO-	3-furyl	R_aCOO-
ibueCO-	2-thienyl	R_aCOO-
ibueCO-	3-thienyl	R_aCOO-
ibueCO-	2-pyridyl	R_aCOO-
ibueCO-	3-pyridyl	R_aCOO-
ibueCO-	4-pyridyl	R_aCOO-
ibueCO-	isobutenyl	R_aCOO-
ibueCO-	isopropyl	R_aCOO-
ibueCO-	cyclopropyl	R_aCOO-
ibueCO-	cyclobutyl	R_aCOO-
ibueCO-	cyclopentyl	R_aCOO-
ibueCO-	phenyl	R_aCOO-
iBuCO-	2-furyl	R_aCOO-
iBuCO-	3-furyl	R_aCOO-
iBuCO-	2-thienyl	R_aCOO-
iBuCO-	3-thienyl	R_aCOO-
iBuCO-	2-pyridyl	R_aCOO-
iBuCO-	3-pyridyl	R_aCOO-
iBuCO-	4-pyridyl	R_aCOO-
iBuCO-	isobutenyl	R_aCOO-
iBuCO-	isopropyl	R_aCOO-

iBuCO-	cyclopropyl	R_aCOO-
iBuCO-	cyclobutyl	R_aCOO-
iBuCO-	cyclopentyl	R_aCOO-
iBuCO-	phenyl	R_aCOO-
iBuOCO-	2-furyl	R_aCOO-
iBuOCO-	3-furyl	R_aCOO-
iBuOCO-	2-thienyl	R_aCOO-
iBuOCO-	3-thienyl	R_aCOO-
iBuOCO-	2-pyridyl	R_aCOO-
iBuOCO-	3-pyridyl	R_aCOO-
iBuOCO-	4-pyridyl	R_aCOO-
iBuOCO-	isobutenyl	R_aCOO-
iBuOCO-	isopropyl	R_aCOO-
iBuOCO-	cyclopropyl	R_aCOO-
iBuOCO-	cyclobutyl	R_aCOO-
iBuOCO-	cyclopentyl	R_aCOO-
iBuOCO-	phenyl	R_aCOO-
iPrOCO-	2-furyl	R_aCOO-
iPrOCO-	3-furyl	R_aCOO-
iPrOCO-	2-thienyl	R_aCOO-
iPrOCO-	3-thienyl	R_aCOO-
iPrOCO-	2-pyridyl	R_aCOO-
iPrOCO-	3-pyridyl	R_aCOO-
iPrOCO-	4-pyridyl	R_aCOO-
iPrOCO-	isobutenyl	R_aCOO-
iPrOCO-	isopropyl	R_aCOO-
iPrOCO-	cyclopropyl	R_aCOO-
iPrOCO-	cyclobutyl	R_aCOO-
iPrOCO-	cyclopentyl	R_aCOO-
iPrOCO-	phenyl	R_aCOO-
nPrOCO-	2-furyl	R_aCOO-

nPrOCO-	3-furyl	R_aCOO-
nPrOCO-	2-thienyl	R_aCOO-
nPrOCO-	3-thienyl	R_aCOO-
nPrOCO-	2-pyridyl	R_aCOO-
nPrOCO-	3-pyridyl	R_aCOO-
nPrOCO-	4-pyridyl	R_aCOO-
nPrOCO-	isobutenyl	R_aCOO-
nPrOCO-	isopropyl	R_aCOO-
nPrOCO-	cyclopropyl	R_aCOO-
nPrOCO-	cyclobutyl	R_aCOO-
nPrOCO-	cyclopentyl	R_aCOO-
nPrOCO-	phenyl	R_aCOO-
nPrCO-	2-furyl	R_aCOO-
nPrCO-	3-furyl	R_aCOO-
nPrCO-	2-thienyl	R_aCOO-
nPrCO-	3-thienyl	R_aCOO-
nPrCO-	2-pyridyl	R_aCOO-
nPrCO-	3-pyridyl	R_aCOO-
nPrCO-	4-pyridyl	R_aCOO-
nPrCO-	isobutenyl	R_aCOO-
nPrCO-	isopropyl	R_aCOO-
nPrCO-	cyclopropyl	R_aCOO-
nPrCO-	cyclobutyl	R_aCOO-
nPrCO-	cyclopentyl	R_aCOO-
nPrCO-	phenyl	R_aCOO-
tBuOCO-	cyclopentyl	EtCOO-
benzoyl	3-furyl	EtCOO-
benzoyl	2-thienyl	EtCOO-
benzoyl	2-pyridyl	EtCOO-
benzoyl	3-pyridyl	EtCOO-
benzoyl	4-pyridyl	EtCOO-

benzoyl	isobutenyl	EtCOO-
benzoyl	isopropyl	EtCOO-
benzoyl	cyclopropyl	EtCOO-
benzoyl	cyclobutyl	EtCOO-
benzoyl	cyclopentyl	EtCOO-
benzoyl	phenyl	EtCOO-
2-FuCO-	3-furyl	EtCOO-
2-FuCO-	3-thienyl	EtCOO-
2-FuCO-	2-pyridyl	EtCOO-
2-FuCO-	3-pyridyl	EtCOO-
2-FuCO-	4-pyridyl	EtCOO-
2-FuCO-	isobutenyl	EtCOO-
2-FuCO-	isopropyl	EtCOO-
2-FuCO-	cyclopropyl	EtCOO-
2-FuCO-	cyclobutyl	EtCOO-
2-FuCO-	cyclopentyl	EtCOO-
2-FuCO-	phenyl	EtCOO-
2-ThCO-	3-furyl	EtCOO-
2-ThCO-	3-thienyl	EtCOO-
2-ThCO-	2-pyridyl	EtCOO-
2-ThCO-	3-pyridyl	EtCOO-
2-ThCO-	4-pyridyl	EtCOO-
2-ThCO-	isobutenyl	EtCOO-
2-ThCO-	isopropyl	EtCOO-
2-ThCO-	cyclopropyl	EtCOO-
2-ThCO-	cyclobutyl	EtCOO-
2-ThCO-	cyclopentyl	EtCOO-
2-ThCO-	phenyl	EtCOO-
2-PyCO-	2-furyl	EtCOO-
2-PyCO-	3-furyl	EtCOO-
2-PyCO-	2-thienyl	EtCOO-

2-PyCO-	3-thienyl	EtCOO-
2-PyCO-	2-pyridyl	EtCOO-
2-PyCO-	3-pyridyl	EtCOO-
2-PyCO-	4-pyridyl	EtCOO-
2-PyCO-	isobutenyl	EtCOO-
2-PyCO-	isopropyl	EtCOO-
2-PyCO-	cyclopropyl	EtCOO-
2-PyCO-	cyclobutyl	EtCOO-
2-PyCO-	cyclopentyl	EtCOO-
2-PyCO-	phenyl	EtCOO-
3PyCO-	2-furyl	EtCOO-
3-PyCO-	3-furyl	EtCOO-
3-PyCO-	3-thienyl	EtCOO-
3-PyCO-	2-pyridyl	EtCOO-
3-PyCO-	3-pyridyl	EtCOO-
3-PyCO-	4-pyridyl	EtCOO-
3-PyCO-	isobutenyl	EtCOO-
3-PyCO-	isopropyl	EtCOO-
3-PyCO-	cyclopropyl	EtCOO-
3-PyCO-	cyclobutyl	EtCOO-
3-PyCO-	cyclopentyl	EtCOO-
3-PyCO-	phenyl	EtCOO-
4-PyCO-	2-furyl	EtCOO-
4-PyCO-	3-furyl	EtCOO-
4-PyCO-	2-thienyl	EtCOO-
4-PyCO-	3-thienyl	EtCOO-
4-PyCO-	2-pyridyl	EtCOO-
4-PyCO-	3-pyridyl	EtCOO-
4-PyCO-	4-pyridyl	EtCOO-
4-PyCO-	isobutenyl	EtCOO-
4-PyCO-	isopropyl	EtCOO-

4-PyCO-	cyclopropyl	EtCOO-
4-PyCO-	cyclobutyl	EtCOO-
4-PyCO-	cyclopentyl	EtCOO-
4-PyCO-	phenyl	EtCOO-
C_4H_7CO-	3-furyl	EtCOO-
C_4H_7CO-	3-thienyl	EtCOO-
C_4H_7CO-	2-pyridyl	EtCOO-
C_4H_7CO-	3-pyridyl	EtCOO-
C_4H_7CO-	4-pyridyl	EtCOO-
C_4H_7CO-	isobutenyl	EtCOO-
C_4H_7CO-	isopropyl	EtCOO-
C_4H_7CO-	cyclopropyl	EtCOO-
C_4H_7CO-	cyclobutyl	EtCOO-
C_4H_7CO-	cyclopentyl	EtCOO-
C_4H_7CO-	phenyl	EtCOO-
EtOCO-	3-furyl	EtCOO-
EtOCO-	3-thienyl	EtCOO-
EtOCO-	2-pyridyl	EtCOO-
EtOCO-	3-pyridyl	EtCOO-
EtOCO-	4-pyridyl	EtCOO-
EtOCO-	isobutenyl	EtCOO-
EtOCO-	isopropyl	EtCOO-
EtOCO-	cyclopropyl	EtCOO-
EtOCO-	cyclobutyl	EtCOO-
EtOCO-	cyclopentyl	EtCOO-
EtOCO-	phenyl	EtCOO-
ibueCO-	2-furyl	EtCOO-
ibueCO-	3-furyl	EtCOO-
ibueCO-	2-thienyl	EtCOO-
ibueCO-	3-thienyl	EtCOO-
ibueCO-	2-pyridyl	EtCOO-

ibueCO-	3-pyridyl	EtCOO-
ibueCO-	4-pyridyl	EtCOO-
ibueCO-	isobutenyl	EtCOO-
ibueCO-	isopropyl	EtCOO-
ibueCO-	cyclopropyl	EtCOO-
ibueCO-	cyclobutyl	EtCOO-
ibueCO-	cyclopentyl	EtCOO-
ibueCO-	phenyl	EtCOO-
iBuCO-	2-furyl	EtCOO-
iBuCO-	3-furyl	EtCOO-
iBuCO-	2-thienyl	EtCOO-
iBuCO-	3-thienyl	EtCOO-
iBuCO-	2-pyridyl	EtCOO-
iBuCO-	3-pyridyl	EtCOO-
iBuCO-	4-pyridyl	EtCOO-
iBuCO-	isobutenyl	EtCOO-
iBuCO-	isopropyl	EtCOO-
iBuCO-	cyclopropyl	EtCOO-
iBuCO-	cyclobutyl	EtCOO-
iBuCO-	cyclopentyl	EtCOO-
iBuCO-	phenyl	EtCOO-
iBuOCO-	2-pyridyl	EtCOO-
iBuOCO-	3-pyridyl	EtCOO-
iBuOCO-	4-pyridyl	EtCOO-
iBuOCO-	isobutenyl	EtCOO-
iBuOCO-	isopropyl	EtCOO-
iBuOCO-	cyclobutyl	EtCOO-
iBuOCO-	cyclopentyl	EtCOO-
iBuOCO-	phenyl	EtCOO-
iPrOCO-	3-furyl	EtCOO-
iPrOCO-	3-thienyl	EtCOO-

iPrOCO-	2-pyridyl	EtCOO-
iPrOCO-	3-pyridyl	EtCOO-
iPrOCO-	4-pyridyl	EtCOO-
iPrOCO-	isobutenyl	EtCOO-
iPrOCO-	isopropyl	EtCOO-
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iPrOCO-	cyclobutyl	EtCOO-
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nPrOCO-	2-thienyl	EtCOO-
nPrOCO-	3-thienyl	EtCOO-
nPrOCO-	2-pyridyl	EtCOO-
nPrOCO-	3-pyridyl	EtCOO-
nPrOCO-	4-pyridyl	EtCOO-
nPrOCO-	isobutenyl	EtCOO-
nPrOCO-	isopropyl	EtCOO-
nPrOCO-	cyclopropyl	EtCOO-
nPrOCO-	cyclobutyl	EtCOO-
nPrOCO-	cyclopentyl	EtCOO-
nPrOCO-	phenyl	EtCOO-
nPrCO-	3-furyl	EtCOO-
nPrCO-	3-thienyl	EtCOO-
nPrCO-	2-pyridyl	EtCOO-
nPrCO-	3-pyridyl	EtCOO-
nPrCO-	4-pyridyl	EtCOO-
nPrCO-	isobutenyl	EtCOO-
nPrCO-	isopropyl	EtCOO-
nPrCO-	cyclopropyl	EtCOO-
nPrCO-	cyclobutyl	EtCOO-

nPrCO-	cyclopentyl	EtCOO-
nPrCO-	phenyl	EtCOO-

Example 4

Following the processes described in Example 1 and elsewhere herein, the following specific taxanes having structural formula 15 may be prepared, wherein R_{10} is hydroxy and R_7 in each of the series (that is, each of series "A" through "K") is as previously defined, including wherein R_7 is $R_{7a}COO$- and R_{7a} is (i) substituted or unsubstituted, preferably unsubstituted, C_2 to C_8 alkyl (straight, branched or cyclic), such as ethyl, propyl, butyl, pentyl, or hexyl; (ii) substituted or unsubstituted, preferably unsubstituted, C_2 to C_8 alkenyl (straight, branched or cyclic), such as ethenyl, propenyl, butenyl, pentenyl or hexenyl; (iii) substituted or unsubstituted, preferably unsubstituted, C_2 to C_8 alkynyl (straight or branched) such as ethynyl, propynyl, butynyl, pentynyl, or hexynyl; (iv) substituted or unsubstituted, preferably unsubstituted, phenyl; or (v) substituted or unsubstituted, preferably unsubstituted, heteroaromatic such as furyl, thienyl, or pyridyl.

In the "A" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), and R_7 and R_{10} each have the beta stereochemical configuration.

In the "B" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

In the "C" series of compounds, X_{10} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{9a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "D" and "E" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl,

thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), and R_7, R_9 (series D only) and R_{10} each have the beta stereochemical configuration.

In the "F" series of compounds, X_{10}, R_{2a} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "G" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

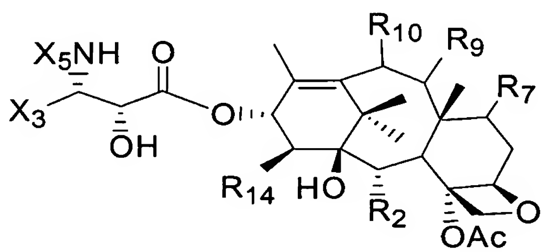
In the "H" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

In the "I" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

In the "J" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "K" series of compounds, X_{10}, R_{2a} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitued furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstitued furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

Any substituents of each X_3, X_5, R_2, R_7, and R_9 may be hydrocarbyl or any of the heteroatom containing substituents selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.



(15)

Series	X_5	X_3	R_7	R_2	R_9	R_{14}
A1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	O	H
A2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	O	H
A3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	O	H
A4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	O	H
A5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	O	H
A6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	O	H
A7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	O	H

A8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	O	H
A9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	O	H
A10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	O	H
A11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	O	H
A12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	O	H
B1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	H
B2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	H
B3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	H
B4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	H
B5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	H
B6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	H
B7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	H
B8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	H

B9	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkenyl	R_{7a}COO-	R_{2a}COO-	O	H
B10	-COOX$_{10}$	optionally substituted C_2 to C_8 alkynyl	R_{7a}COO-	R_{2a}COO-	O	H
B11	-COX$_{10}$	optionally substituted C_2 to C_8 alkynyl	R_{7a}COO-	R_{2a}COO-	O	H
B12	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkynyl	R_{7a}COO-	R_{2a}COO-	O	H
C1	-COOX$_{10}$	heterocyclo	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C2	-COX$_{10}$	heterocyclo	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C3	-CONHX$_{10}$	heterocyclo	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C4	-COOX$_{10}$	optionally substituted C_2 to C_8 alkyl	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C5	-COX$_{10}$	optionally substituted C_2 to C_8 alkyl	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C6	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkyl	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C7	-COOX$_{10}$	optionally substituted C_2 to C_8 alkenyl	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C8	-COX$_{10}$	optionally substituted C_2 to C_8 alkenyl	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H
C9	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkenyl	R_{7a}COO-	C_6H_5COO-	R_{9a}COO-	H

C10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
C12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	$R_{9a}COO-$	H
D1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	H
D2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	H
D3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	H
D4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
D5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
D6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
D7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
D8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
D9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
D10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	H

D11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
D12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	H
E1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	O	OH
E2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	O	OH
E3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	O	OH
E4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	O	OH

E12	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkynyl	R_{7a}COO-	C_6H_5COO-	O	OH
F1	-COOX$_{10}$	heterocyclo	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F2	-COX$_{10}$	heterocyclo	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F3	-CONHX$_{10}$	heterocyclo	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F4	-COOX$_{10}$	optionally substituted C_2 to C_8 alkyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F5	-COX$_{10}$	optionally substituted C_2 to C_8 alkyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F6	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F7	-COOX$_{10}$	optionally substituted C_2 to C_8 alkenyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F8	-COX$_{10}$	optionally substituted C_2 to C_8 alkenyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F9	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkenyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F10	-COOX$_{10}$	optionally substituted C_2 to C_8 alkynyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F11	-COX$_{10}$	optionally substituted C_2 to C_8 alkynyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
F12	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkynyl	R_{7a}COO-	R_{2a}COO-	R_{9a}COO-	H
G1	-COOX$_{10}$	heterocyclo	R_{7a}COO-	R_{2a}COO-	OH	H
G2	-COX$_{10}$	heterocyclo	R_{7a}COO-	R_{2a}COO-	OH	H

G3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
H1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH

H5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
I1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH

I7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
J1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH

J8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
K1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH

K9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH

Example 5

In Vitro cytotoxicity measured by the cell colony formation assay

Four hundred cells (HCT116) were plated in 60 mm Petri dishes containing 2.7 mL of medium (modified McCoy's 5a medium containing 10% fetal bovine serum and 100 units/mL penicillin and 100 g/mL streptomycin). The cells were incubated in a CO_2 incubator at 37 °C for 5 h for attachment to the bottom of Petri dishes. The compounds identified in Example 2 were made up fresh in medium at ten times the final concentration, and then 0.3 mL of this stock solution was added to the 2.7 mL of medium in the dish. The cells were then incubated with drugs for 72 h at 37 ° C. At the end of incubation the drug-containing media were decanted, the dishes were rinsed with 4 mL of Hank's Balance Salt Solution (HBSS), 5 mL of fresh medium was added, and the dishes were returned to the incubator for colony formation. The cell colonies were counted using a colony counter after incubation for 7 days. Cell survival was calculated and the values of ID50 (the drug concentration producing 50% inhibition of colony formation) were determined for each tested compound.

Compound	IN VITRO ID 50 (nm) HCT116
taxol	2.1
docetaxel	0.6
1351	<1
1364	<10
1372	26.1
1386	<1
1393	<1
1401	<1
1418	<1
1424	<1
1434	<10
1447	<10
1458	<10
3069	<1
3082	<1
3171	<1
3196	<10
3232	<1
3327	<10
3388	<10
3444	<1
3479	<1
3555	<10
3560	<1
3611	<1
3629	<1
3632	<1
3708	<1

3713	<10
4017	<10
4044	<1
4106	<10
4135	<1
4175	<10
4219	29.0
4256	<1
4283	<1
4290	<10
4312	<1
4388	<1
4394	<1
4406	<1
4446	<1
4499	<1
4544	<10
4600	<10
4616	<1
4737	<1
4757	<1
6171	<10
6131	<1
5989	<10
6141	<1
6181	<1
6040	<10
6121	<10
6424	21.7
6212	<1
6282	<10

6252	<1
6343	<10
6272	<1
6202	<1
4454	<1
4414	<1
6333	<1
6686	<1
6363	<10
4787	<10
4828	<10
4898	<1
4939	<1
5020	<1
5030	<1
5191	<10
5202	<10
5070	<10
5080	<1
5121	21.1
5131	<10

Example 6

Preparation of Solutions for Oral Administration

Solution 1: Antitumor compound 1393 was dissolved in ethanol to form a solution containing 140 mg of the compound per ml of solution. An equal volume of Cremophor® EL solution was added to the solution while stirring to form a solution containing 70 mg of compound 1393 per ml. This solution was diluted using 9 parts by weight of saline to form a pharmaceutically acceptable solution for administration to a patient.

Solution 2: Antitumor compound 1458 was dissolved in ethanol to form a solution containing 310 mg of the compound per ml of solution. An equal volume of Cremophor® EL solution was added to the solution while stirring to form a solution containing 155 mg of compound 1458 per ml. This solution was diluted using 9 parts by weight of saline to form a pharmaceutically acceptable solution for administration to a patient.

Solution 3: Antitumor compound 1351 was dissolved in ethanol to form a solution containing 145 mg of the compound per ml of solution. An equal volume of Cremophor® EL solution was added to the solution while stirring to form a solution containing 72.5 mg of compound 1351 per ml. This solution was diluted using 9 parts by weight of saline to form a pharmaceutically acceptable solution for administration to a patient.

Solution 4: Antitumor compound 4017 was dissolved in ethanol to form a solution containing 214 mg of the compound per ml of solution. An equal volume of Cremophor® EL solution was added to the solution while stirring to form a solution containing 107 mg of compound 4017 per ml. This solution was diluted using 9 parts by weight of saline to form a pharmaceutically acceptable solution for administration to a patient.

Solution 5: Antitumor compound 1393 was dissolved in 100% ethanol then mixed with an equal volume of Cremophor® EL solution to form a solution containing 70 mg of compound 1393 per ml. This solution was diluted using 9 parts by weight of D%W (an aqueous solution containing 5 % weight by volume of dextrose) or 0.9% saline to form a pharmaceutically acceptable solution for administration to a patient.

Example 7

Preparation of a Suspension Containing Compound 1393 for Oral Administration

An oral composition of antitumor compound 1393 was prepared by suspending 25 mg of compound 1393 as a fine powder in one ml of carrier containing 1% carboxymethylcellulose (CMC) in deionized water.

Example 8

Preparation of a Tablet Containing Compound 1393 for Oral Administration

Antitumor compound 1393 (100 mg) was dissolved in methylene chloride (2 ml) and Cremophor® EL solution (100mg) was added. The methylene chloride was evaporated under vacuum to form a glass. Microcrystalline cellulose (600 mg) was added to the glass and mixed to form a powder which can be processed to form a tablet.

Example 9

Preparation of Emulsions Containing Compound 1393 for Parenteral Administration

Emulsion 1: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 40 mg of compound 1393 per ml of the solution. The solution was then diluted with 19 parts by weight of Liposyn® II (20%) with stirring to form an emulsion containing 2 mg of compound 1393 per ml for parenteral administration.

Emulsion 2: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 40 mg of compound 1393 per ml of the solution. The solution was then diluted with 19 parts by weight of Liposyn® III (2%) with stirring to form an emulsion containing 2 mg of compound 1393 per ml for parenteral administration.

Emulsion 3: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing mg of compound 1393 per ml of the solution. The solution was then diluted with 9 parts by weight of Liposyn® III (2%) with stirring to form an emulsion containing 4 mg of compound 1393 per ml for parenteral administration.

Example 10

Preparation of Solutions Containing Compound 1393 for Parenteral Administration

Solution 1: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 140 mg of compound 1393 per ml. The solution was then diluted with an equal volume of Cremophor® EL solution with stirring and was then diluted with 9 parts by weight of normal saline to form a solution containing 7 mg of compound 1393 per ml of solution for parenteral administration.

Solution 2: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 140 mg of compound 1393 per ml of the solution. The solution was then diluted with an equal volume of Cremophor® EL solution with stirring and was then diluted with 4 parts by weight of normal saline to form a solution containing 11.7 mg of compound 1393 per ml of solution for parenteral administration.

Solution 3: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 140 mg of compound 1393 per ml of the solution. The solution was then diluted with an equal volume of Cremophor® EL solution with stirring and was then diluted with 2.33 parts by weight of normal saline to form a solution containing 16.2 mg of compound 1393 per ml of solution for parenteral administration.